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A Phase 3 Double-Blind Placebo-Controlled Evaluation of Sofosbuvir/Velpatasvir Fixed Dose Combination for 12 Weeks in Naïve and Experienced Genotype 1, 2, 4, 5, 6 HCV Infected Patients with and without cirrhosis: Results of the ASTRAL-1 Study

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Introduction: Velpatasvir (VEL, GS-5816) is a pangenotypic HCV NS5A inhibitor. In Phase 2 studies, the combination of sofosbuvir (SOF) and VEL for 12 weeks resulted in high SVR12 in patients with genotype 1-6 HCV infection. This Phase 3 study evaluated treatment with a fixed dose combination of SOF/VEL for 12 weeks in patients with genotype 1, 2, 4, 5, or 6 HCV infection (ClinicalTrials.gov Identifier: NCT02201940).

Methods: Patients with genotype 1, 2, 4, or 6 chronic HCV infection were randomized 5:1 to received SOF/VEL (400 mg /100 mg daily) or placebo for 12 weeks. Patients with genotype 5 infection were enrolled to the SOF/VEL treatment group. Patients with genotype 3 infection were evaluated in a separate study. The primary efficacy analysis was an evaluation of the superiority of SVR12 for the SOF/VEL-treated patients to a pre-specified SVR12 goal of 85%. Secondary endpoints included safety/tolerability, resistance, and additional efficacy outcomes.

Results: 740 patients were enrolled at 81 sites in North America, Europe and Hong Kong: 60% male, 79% white, 30% IL28B CC genotype, 32% treatment-experienced (TE), and 19% compensated cirrhosis. Of the 624 patients treated with SOF/VEL, the genotype distribution was 53% GT1, 17% GT2, 19% GT4, 6% GT5 and 7% GT6. Overall SVR12 for SOF/VEL-treated patients was 99.0% (95% confidence interval 97.9% to 99.6%) and the study met its primary efficacy endpoint ($p< 0.001$). SVR12 rates by HCV genotype are presented in the table. Two of 325 patients (0.6%) with genotype 1 infection, including 1 of 73 with cirrhosis, had virologic relapse: 1 genotype 1a treatment-naïve non-cirrhotic and 1 genotype 1b treatment-experienced with cirrhosis. No patients with genotype 2, 4, 5, or 6, including 48 with cirrhosis, had virologic failure. Four patients did not achieve SVR12 for non-virologic reasons (eg. lost to follow-up). Overall, the type, frequency and severity of AEs and laboratory abnormalities were similar in the SOF/VEL-treated patients compared with the 116 placebo-treated patients. Three patients discontinued treatment due to adverse events, 1 treated with SOF/VEL and 2 with placebo. One SOF/VEL-treated patient died from an unknown cause 8 days after completion of treatment. Fifteen (2.4%) SOF/VEL-treated patients and no placebo-treated patients experienced SAEs; none was assessed as related to study drug.

Conclusions: Treatment with the once daily, all-oral, single tablet regimen of SOF/VEL for 12 weeks is well tolerated and results in high SVR12 rates in treatment-naïve and treatment-experienced genotype 1, 2, 4, 5, and 6 HCV-infected patients with and without cirrhosis.

HCV Genotype	Total (N = 624)	GT 1 (N = 328)	GT 2 (N = 104)	GT 4 (N = 116)	GT 5 (N = 35)	GT 6 (N = 41)
Cirrhosis %, (n/N)	19.4% (121/624)	22.3% (73/328)	9.6% (10/104)	23.3% (27/116)	14.3% (5/35)	14.6% (6/41)
SVR12 %, (n/N)	99.0% (618/624)	98.5% (323/328)	100.0% (104/104)	100.0% (116/116)	97.1% (34/35)	100.0% (41/41)

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